



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/892,227 | 06/25/2001 | Hermann Bujard | BBI-013C2CN2 | 7548 |

959 7590 10/03/2002

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

[REDACTED] EXAMINER

PARAS JR, PETER

| ART UNIT | PAPER NUMBER |
|----------|--------------|
| 1632 | [REDACTED] |

DATE MAILED: 10/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/892,227 | BUJARD ET AL. | |
| | Examiner | Art Unit | |
| | Peter Paras | 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on _____.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 23-34 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 23-34 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) Interview Summary (PTO-413) Paper No(s) _____.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: _____.

Applicant's preliminary amendments received on 6/25/02 and 3/28/02 have been entered. Claims 1-22 have been cancelled. New claims 23-34 have been added. Claims 23-34 are pending and are under current consideration.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 23-34, drawn to transgenic organisms, wherein the transgenic organisms are non-human animals, classified in class 800, subclass 13.
- II. Claims 23-34, drawn to transgenic organisms, wherein the transgenic organisms are plants, classified in class 800, subclass 295.

Inventions I and II are distinct. Inventions are distinct if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are products that are not capable of use together and have different modes of operation, different functions, and different effects. The inventions of Groups I and II are products that have different chemical structures, as they appear to be from different taxonomical kingdoms, animals and plants, respectively. As such their chemical structures are divergent. Moreover, the products of Groups I and II appear to have different effects, the transgenic non-human animal of Group I could be used as a model of mammalian disease, whereas the transgenic plant of Group II could not be used as a model of mammalian disease, but rather could be used as a model of plant disease. In addition, the products of Groups I and II could be

used in materially different methods that have different technical considerations. For example, the transgenic non-human animal of Group I could be used for screening candidate agents that may be able to treat a mammalian disorder while the transgenic plant of Group II could be used to produce genetically altered produce for consumption. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and separate search requirement and different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Giulio DeConti on 9/30/02 a provisional election was made with traverse to prosecute the invention of Group I, claims 23-34 with respect to non-human animals. Affirmation of this election must be made by applicant in replying to this Office action. Claims 23-34, to the extent that they read on transgenic plants, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: 4A-4D; 5A-5D; 9D-9H; and 10C-10F. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 23 is objected to because of the following informalities: in line 7, the phrase "is a" is missing from between the terms "which" and "Tet" repressor". Appropriate correction is required.

Claims 23-34 are objected to for reading on non-elected subject matter. See the restriction requirement above. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 23-32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 23-32 are directed to transgenic organisms, the scope of which encompasses a human being. A human being is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be

remedial for claim 10. See 1077 O.G. 24, April 21, 1987. Although the elected invention is directed to non-human transgenic animals, the claims as written encompass transgenic humans as stated above.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention to the extent of a transgenic mouse, does not reasonably provide enablement for all other transgenic organisms (which are non-human animals in accordance with the elected invention) embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to transgenic organisms having a transgene integrated into the genome of the organism and also having a tet operator-linked gene in the genome of the organism, wherein: the transgene comprises a transcriptional regulatory element functional in cells of the organism operatively linked to a polynucleotide sequence encoding a fusion protein which activates transcription of said tet operator-linked gene, the fusion protein comprises a tet repressor operatively linked to a polypeptide that activates transcription in eukaryotic cells, said tet operator-linked gene,

which is a gene of interest, confers a detectable and functional phenotype on the organism when expressed in cells of the organism, said transgene is expressed at a level to activate transcription of the tet operator-linked gene, wherein presence of tetracycline can down-regulate expression of the tet operator-linked gene. The claims are further directed integration of the transgene at a predetermined location in the genome of the organism and wherein the polypeptide is a transcription activation domain of herpes simplex virion protein 16.

The specification discusses that the invention features a system for regulating expression of eukaryotic gene using components of the Tet repressor/operator/inducer system in a transgenic animal. See page 2. The specification discusses that the invention features a transgenic animal in which transcription of a nucleotide sequence operably linked to at least one tet operator sequence is stimulated by a tetracycline (tc)-controllable transcriptional activator fusion protein (tTA), wherein tTA is comprised of two polypeptides, the Tet repressor and a polypeptide that can indirectly or indirectly activate transcription in eukaryotes. See pages 2, 10, and 11. The specification also contemplates that the transgene is integrated at a predetermined location within a chromosome (see page 19, for example). While the specification provides extensive teachings, specific guidance, and working examples pertaining to the creation of a transgenic mouse comprising such a tetracycline inducible transcription system (see pages 49-50), the specification fails to provide any relevant teachings or specific guidance with regard to the generation of the other (non-human transgenic animals consistent with the elected invention) transgenic organisms with their corresponding

phenotypes embraced by the claims (as is consistent with the discussion of the specification). Furthermore, the specification fails to even describe any particular type of phenotype exhibited by a transgenic non-human animal of the invention, only that such an animal would be useful for producing a protein (for collection, for example, see page 28, 2nd paragraph of the specification). In view of the lack of guidance provided by the specification it would have required undue experimentation to make and use the other transgenic (non-human animals consistent with the elected invention) organisms as claimed.

In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed transgenic organism (which is a non-human animal as is consistent with the elected invention) having cells which harbor a tet operator-linked transgene is one that expresses the transgene at a level sufficient to result in a phenotype (*i.e.*, it is unknown what other purpose the transgenic non-human animal would serve if the transgene is not expressed at a sufficient level for a resulting phenotype).

With regard to claims 23-26 and 31-34, while the specification has provided guidance and working examples directed to the creation of a transgenic mouse, by pronuclear injection based on random transgene integration, whose genome comprises a transgene and a tet operator-linked gene the specification fails to provide any relevant teachings, guidance, working examples with regard to the production of the other

transgenic organisms (non-human animals as is consistent with the elected invention) as claimed. One of skill would not be able to rely on the state of the transgenic art for an attempt to produce the other transgenic non-human animals whose genomes comprise a transgene and a tet-operator-linked gene that are broadly encompassed by the claims. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that “[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior.” See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); e.g., specific promoters, presence or absence of introns, etc. As such guidance is lacking in the

instant specification for the production of the other transgenic non-human animals and their corresponding phenotypes embraced by the claims.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and

rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of transgenic non-human animals other than mouse whose genomes comprise a transgene and a tet operator-linked gene, it would have required undue experimentation to predict the results achieved in any of the other non-human animals and their phenotype corresponding phenotypes embraced by the claims.

Claims 27-30 are directed to integration of the transgene at a predetermined location in the genome of a transgenic organism (which is a non-human animal as is consistent with the elected invention). This claim limitation clearly read on introduction of the transgene by homologous recombination into the genome of ES cells, which are then used to create chimeric animals when taken with the teachings of the specification. See page 11 for example. It is noted that although the claim does not specifically require the use of embryonic stem (ES) cells for the production of the claimed transgenic non-human animal, the specification contemplates the use of embryonic stem (ES) cells for the generation of transgenic non-human animals. See pages 18-19, for example. However, the prior and post-filing art are replete with references, which indicate that ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. (J. Mol. Med., 1997, page 214, Summary), who supports this observation. In addition, Seemark (Reproduction, Fertility and Development, 1994) discloses that totipotency for ES cell

technology in many livestock species has not been demonstrated (page 653, Abstract). Mullins et al. disclose that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims encompass a transgenic non-human animals which may be generated by the introduction of a transgene into an ES cell, and as the specification fails to teach the establishment of true ES cells for use in the production of transgenic non-human animals other than mouse, the state of the art supports that only mouse ES cells were available for use for production of transgenic animals.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals other than mouse, the absence of working examples for the demonstration or correlation to the production of a transgenic non-human animal other than mouse expressing a tet operator-lined gene, wherein expression of the gene must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to transgene behavior in transgenic non-human animals, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to organisms that are non-human animals as elected, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 23-34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 5,859,301. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims encompass transgenic organisms, which are non-human animals in accordance with the elected invention, in particular mice, whose genomes comprise a transgene and a tet operator-linked gene as claimed. The claims of the instant application are directed to a genus of transgenic organisms, which are non-human animals in accordance with the elected invention, while the claims of US 5,859,301 are directed to transgenic mice, which would anticipate the instant claims.

Furthermore, the transgene comprises a transcriptional regulatory element operatively linked to a polynucleotide sequence encoding a fusion protein that comprises a Tet repressor operably linked to a polypeptide which directly or indirectly activates transcription of said tet operator linked gene. The claims of US 5,859,301 recite a tetracycline-controllable transactivator fusion protein (tTA) while the instant

claims recite a fusion protein, which activates transcription of said tet operator linked gene. The specification of the instant application has defined the fusion protein, which activates transcription of said tet operator linked gene, as a tTA fusion protein. See the specification on page 2. In any event in both sets of claims the fusion protein comprises a Tet repressor operatively linked to a polypeptide, which directly or indirectly activates transcription of the tet operator linked gene. Claims 2, 8, and 14 of US 5,859,301 recite that the Tet repressor is a Tn10-derived Tet repressor. The instant specification has defined Tet repressors as encompassing Tn10-derived Tet repressors). See page 2. Finally claims 6 and 12 of US 5,859,301 are directed to methods of inhibiting transcription of the tet operator-linked gene comprising administering tetracycline or a tetracycline analogue. Claim 23 of the instant application meets this limitation by reciting in the last three lines that "the level of expression of the tet operator-linked gene can be downmodulated by administering tetracycline or a tetracycline analogue".

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Patsy Zimmerman whose telephone number is (703) 308-0009.

Peter Paras, Jr.
Art Unit 1632

Pete Paras
Art Unit 1632